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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,849	06/27/2002	William Hugold Velander	TRANS 1	2472

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EXAMINER
HAMA, JOANNE

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
09/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/049,849	VELANDER, WILLIAM HUGOLD	
	Examiner	Art Unit	
	JOANNE HAMA	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40,42,44,46,56-58 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40,42,44,46,56-58 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to the Non-Final Rejection of February 4, 2009 on August 3, 2009. Claims 1-39, 41, 43, 45, 47-55, 59, 60 are cancelled.

Claims 40, 42, 44, 46, 56-58, 61, drawn to a composition comprising milk derived from a transgenic mammal and a recombinant human prothrombin, wherein the Gla domain of prothrombin is gamma-carboxylated, are under consideration.

Maintained Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40 and 61 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al., US Patent 4,873,316, patented October 10, 1989, in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-6734, previously cited, Seegers et al., 1950, Blood, 5: 421-433, previously cited, van Cott and Velander, 1998, Expert Opinion on Investigational Drugs, 7: 1683-1690, previously cited, Velander et al., 1992, PNAS, USA, 89: 12003-12007, see IDS, for reasons of record, February 4, 2009.

Claims 40, 42, 44, 46, 56, and 58 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al., US Patent 4,873,316, patented October 10,

1989, in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-6734 previously cited, Le Bonniec et al., 1991, The Journal of Biochemistry, 266: 13796-13803, previously cited, Velander et al., 1992, PNAS, USA, 89: 12003-12007, see IDS, for reasons of record, February 4, 2009.

Claims 40 and 57 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al., US Patent 4,873,316, patented October 10, 1989, in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-6734, previously cited, in view of Seegers et al., 1950, Blood 5: 421-433, previously cited, Le Bonniec et al., 1991, The Journal of Biochemistry, 266: 13796-13803, previously cited, Velander et al., 1992, PNAS, USA, 89: 12003-12007, see IDS, for reasons of record, February 4, 2009.

Applicant's arguments filed August 3, 2009 have been fully considered but they are not persuasive.

Applicant indicates that the combination of Meade et al. and Jorgensen et al. would hardly result in an "efficient means" for transgenic protein expression/collection/isolation because the expressed protein concentrations are limited to micrograms/milliliter, much too low for commercial exploitation. Applicant specifically pointed out that low yield compositions derived from in vitro culture methods (such as that of Jorgensen et al. are disadvantageous. Applicant indicates that the specification teaches that attempts to culture genetically altered cells to produce prothrombin polypeptides have produced uneconomically low yields and, generally, preparations of low specificity (specification, page 6, lines 5-7). KSR requires an Examiner to provide

an explicit analysis to support the obviousness rejection and in the instant case, none of the cited references teach expression or recombinant prothrombin polypeptide at a concentration of 0.5mg/ml (Applicant's emphasis, Applicant's response, pages 5-6). In response, this is not persuasive. The Examiner did not solely depend on Jorgensen et al. to teach the claimed invention. Rather, the Examiner depended on the combination of Meade et al. and Jorgensen et al. for teaching that recombinant human prothrombin can be made in the milk of transgenic mammals. The Examiner relied on Meade et al. for teaching an efficient means of making large quantities of recombinant protein in milk and that any protein may be produced using their method (Meade et al., cols. 1-3; see also, Office Action, August 25, 2008, page 4-5). Meade et al. do not teach the sequence of human prothombin. Jorgensen et al. teach that an expression vector comprising the coding sequence of human prothrombin was used to express recombinant prothrombin. An artisan would have combined the two teachings in order to arrive at recombinant human prothrombin in milk. An artisan would have done so because Meade et al. teach that transgenic mammals secrete large quantities of a protein of interest in milk. To address the issue of why an artisan would want to make large quantities of prothrombin, Seegers et al. teach that large amounts of prothrombin is required in order to study its role in blood clotting (Seegers et al., page 421, 2nd parag; see also Office Action, August 25, 2008, page 5). With regard to the limitation that recombinant prothrombin is expressed at a concentration of at least 0.5 mg/ml, the Examiner relied on Velander et al., who teach that recombinant protein can be expressed in milk of transgenic pigs at levels as high as 1000ug/ml (i.e. 1mg/ml)

(Velander et al., page 12005, 1st col., parag. under "Protein Analysis", see also Figure 1). Because Velander et al. teach that transgenic mammals can secrete 1mg/ml of recombinant protein in milk, an artisan would have arrived at a transgenic mammal that secreted recombinant human prothombin in milk at a concentration as high as 1mg/ml.

Applicant indicates that KSR requires an explicit analysis to support the obviousness rejection and that the Examiner has not done so. Merely pointing to single words, without the appropriate context, is whollly insufficient. The Examiner's references are pointed to only for various isolated elements that can only be interpreted as the "mere identification in the prior art of each element" (Applicant's emphasis, Applicant's response, page 6). In response, this is not persuasive. The Examiner has provided an analysis of combining the cited references, see Office Actions of August 25, 2008 and February 4, 2009. The Examiner has relied on Meade et al. for teaching large quantities of recombinant protein in milk; Jorgensen et al. for teaching that the coding sequence of human prothrombin was known; Seegers et al. for teaching that artisans need large quantities of prothrombin for blood clotting studies; and Velander et al. for teaching that mammals can secrete recombinant protein in milk (1000ug/ml=1mg/ml) that is at least 0.5 mg./ml. As such, indicating these teachings in the art such that an artisan arrives at the claimed invention, was an appropriate rejection of the claims.

Applicant indicates the Examiner has not identified within any of the asserted references such that a reasonable expectation of success is apparent. This lack of evidence of success in the asserted references, the Examiner has not met well settled patent law for establishing a "reasonable expectation of success" such that the

references explicitly predict that the recited claims would work (Applicant's emphasis, Applicant's response, page 7). In response, "reasonable expectation of success" does not mean explicit teaching of success. "Obviousness does not require absolute predictability of success." In re O 'Farrell, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988) at 903, 7 USPQ2d at 1681. The Examiner relied on Velander et al. for teaching that transgenic pigs have been shown to express recombinant proteins at concentrations of 1mg/ml. Given this teaching, an artisan would reasonable expect that some transgenic pigs would express recombinant prothrombin at these concentrations.

Applicant indicates that the Examiner has not found all of Applicant's claimed elements to support the asserted reference combination. For example, the Examiner has admitted that Meade et al. does not teach all of the claimed elements, wherein Meade et al. does not indicate that recombinant prothrombin is made in milk. Meade et al. also do not teach the expression of any recombinant protein at levels of 0.5mg/ml, much less prothrombin comprising a fully carboxylated Gla domain (Applicant's emphasis, Applicant's response, page 7). In response, the rejection at hand is not a 102 or a one reference 103. The Examiner has relied on other publications that teach the limitations of the claims.

Applicant indicates that Jorgensen et al. cannot be properly combined with Meade et al. because Jorgensen et al. does not teach a high expression level of completely carboxylated prothrombin. In response, Jorgensen et al. was not relied upon for teaching the concentration of recombinant protein in milk. Jorgensen et al. was relied upon for teaching that the sequence of human prothrombin was known.

Velander et al. was used to teach that transgenic mammals can secrete recombinant protein of interest in milk at concentrations of 1ml/ml.

Applicant indicates that Jorgensen's cell culture technique observed a 40% drop in carboxylated prothrombin at expression levels of 6.5-8.2 ug/ml, when exposed to methotrexate concentrations that artificially increase expression levels. These levels are less than those disclosed in Applicant's specification (Applicant's emphasis, Applicant's response, page 8). In response, the Examiner did not rely on Jorgensen et al. for teaching expression levels of prothrombin that is at least 0.5mg/ml. The Examiner relied on Velander et al. for teaching that high concentration of recombinant protein is secreted in milk and van Cott and Velander who teach that transgenic pigs are able to gamma-carboxylate recombinant proteins excreted in milk (Office Action, June 25, 2008, page 6).

Applicant indicates that a superior and more advantageous composition than either Meade or Jorgensen et al. was made. Applicant refers to page 35, lines 3-10, of the specification, wherein the specification indicates that the yields are substantially better than those previously achieved by other methods. Applicant indicates that well settled case law holds that demonstrated superiority and advantages overcome obviousness (Applicant's emphasis, Applicant's response, page 9). In response, this is not persuasive. High concentrations of recombinant protein secreted in milk were known at the time of filing. With regard to the recombinant protein being completely gamma-carboxylated, van Cott and Velander teach that transgenic pigs have been shown to gamma-carboxylate proteins.

Applicant refers to a citation in Velander et al., PNAS, 89: 12003-12007, 1st col., (Dec. 1992) that indicates that there is no direct correlation between the level of expression in transgenic mice compared to livestock for a given genetic construct.... The choice of employing a cDNA versus a genomic construct to synthesize a given protein in the mammary blad of livestock can become complex. Applicant indicates that Velander et al.'s teaching does not support the Examiner's assumption that just because a WAP promoter produced human protein C at 1mg/ml, that it should be predictable that it would be expected to produce a fully carboxylated prothrombin at 0.5 mg/ml (Applicant's emphasis, Applicant's response, page 10). In response, this is not persuasive. Velander et al.'s teaching indicates that there is variability in the concentration levels of recombinant protein secreted in milk. However, given that there has been an example of transgenic mammals being able to produce recombinant proteins in milk at levels as high as 1mg/ml, it is reasonable for an artisan to make a number of transgenic lines, wherein at least one produces recombinant protein at high levels. It is noted that it is within skill of the artisan to play with conditions such as the set-up of the construct itself (e.g. the promoter) and concentration of DNA that is injected into the fertiilized oocyte, as these are steps of routine optimization. Note, for example, Meade et al. teach a number of promoter that can be used to express recombinant protein in milk (Meade et al., col., 3 1st parag.), and that the construct can comprise a 3' untranslated region (UTR) downstream of the sequence coding for the desired recombinant protein. The UTR stabilizes that RNA transcript of the expression system and thrus increases the yield of desired protein from the expression system

(Meade et al., col. 3, 5th parag.). As such, while Velander et al. teach that the amount of recombinant protein secreted in milk varies from mammal to mammal, the art (e.g. Meade et al.) provide guidance for increasing one's chances at arriving at a mammal that expresses at high levels.

Applicant indicates in the footnote at the bottom of page 10 that the Examiner is not one skilled in the art and that mere opinion of the Examiner on what one skilled in the art might believe does not count. In response, the Examiner is not indicating an opinion in writing the 103 rejection. Rather, the Examiner established a prima facie case of obviousness wherein one must:

(A) determine the scope and contents of the prior art;

(B) ascertain the differences between the prior art and the claims in issue;

(C) determine the level of ordinary skill in the pertinent art; and

(D) evaluate any evidence of secondary considerations.

The Examiner is relying on teachings in the art and is indicating that because the elements in the art provide guidance to arrive at the claimed invention, an artisan would have combined the elements and reasonably predicted to arrive at the claimed invention.

With regard to Seegers et al., Applicant indicates that the Examiner has not shown that Seegers et al. remedies the deficiencies of Meade et al. and Jorgensen et al. by teaching a highly expressed fully carboxylated recombinant prothrombin. As such, claim 40 is patentable. In response, this is not persuasive. Seegers et al. was relied upon to teach the limitation of claim 57, wherein Seegers et al. teach the

processing of prothrombin to thrombin by using sodium citrate (Office Action, June 25, 2008, page 7). It is noted that Seegers et al. was also relied upon for teaching that large amounts of prothrombin is needed to study its role in blood clotting (Office Action, June 25, 2008, page 5). As such, an artisan would have been motivated to make large amounts of prothrombin in the milk of transgenic mammals such that a source of recombinant thrombin would be easy to obtain. With regard to Applicant indicating that Seegers et al. do not remedy the combined teachings of Meade et al. and Jorgensen et al., it is noted that Velander et al. was relied upon for teaching that transgenic mammals have been shown to express high concentrations of recombinant protein in milk (Office Action, February 4, 2009, page 3) and that van Cott and Velander teach that transgenic pigs can gamma-carboxylate recombinant proteins (Office Action, June 25, 2009, page 6).

With regard to van Cott and Velander, Applicant indicates that van Cott et al. were not discussing the gamma-carboxylation of prothrombin, van Cott et al., page 1686, rhc-1687 lhc. Velander et al. does not teach the expression of prothrombin and does not disclose any recombinant expression of at least 0.5mg/ml. Further, van Cott et al. does not even mention prothrombin as a possible protein for expression. van Cott et al. does not provide any evidence that protein C and Factor IX (FIX) were fully carboxylated, only that gamma-carboxylation is better in pigs than in mice. The prothrombin expression level in claim 40 is 5 times superior to that referred to in van Cott et al. (i.e., 0.1g/l/h = 0.1mg/ml/h) (Applicant's emphasis, Applicant's response, page 11). In response, this is not persuasive. With regard to Applicant indicating that van

Cott et al. does not discuss the gamma-carboxylation of prothrombin, the Examiner was relying on van Cott et al. for teaching that pigs had the ability to gamma-carboxylate proteins, such as FIX and protein C and because pigs could gamma-carboxylate proteins, an artisan would have predicted that pigs had the ability to gamma-carboxylate other proteins with a Gla domain, such as prothrombin. With regard to Applicant indicating that van Cott et al. does not indicate prothrobmin as a possible protein of expression in transgenic mammals, the Examiner was not relying on van Cott et al. for this teaching. Rather, the teaching was provided by Seegers et al. who teach that large quantities of prothrombin are required to study blood clotting and Meade et al. for teaching that large amounts of recombinant protein can be produced in milk by transgenic mammals. With regard to van Cott et al. not providing any evidence that protein C and FIX were fully carboxylated and that only gamma-carboxylation was better in pigs than in mice, an artisan would understand that the transgenic pigs were producing fully gamma-carboxylated protein C and FIX as mammalian cells express gamma-carboxylase, the enzyme that can fully gamma-carboxylate clotting factor proteins, such as protein C and prothrombin. For example, see Jorgensen et al. 1987 and Velander et al. 1992 who teach that cells can fully carboxylate proteins with Gla domains. With regard to Applicant indicating that prothombin expression is 5 times superior than that of van Cott et al., it is noted that van Cott et al. was not relied upon for teaching that transgenic mammals can produce 1mg/ml of recombinant protein. That teaching was provided by Velander et al. With regard to Applicant citing van Cott et al. teaching “0.1g/l/h = 0.1mg/ml/h”, it is noted that 0.1g/l/h=100mg/ml/h, and that this is the

rate at which pigs can gamma-carboxylate protein. It is noted that in 1 hour, if a transgenic pig produced 100 mg/ml of protein, it can carboxylate 100mg of protein/ml. This would meet the limitation of the claims.

With regard to Le Bonniec et al., Applicant indicates that Le Bonniec et al. does not remedy the lack of a prima facie case of obviousness in view of the other asserted references discussed above. Le Bonniec et al. do not provide any evidence teaching recombinant prothrobmin in the milk of a transgenic mammal having a concentration of 0.5 mg/ml. In response, Le Bonniec et al. was provided to teach that prothrombin is activated by bovine factor Xa in the presence of bovine factor Va, phospholipids, and calcium (Office Action, June 25, 2008, page 6) (see claim 56). With regard to the teachings of claim 40, the Examiner relied on the combination of teachings of Meade et al., Jorgensen et al., and Velander et al.

Thus, the claims remain rejected.

Conclusion

No claims allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued

examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Mondays, Tuesdays, Thursdays, and Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Joanne Hama/
Primary Examiner
Art Unit 1632